Temsirolimus in the treatment of renal cell carcinoma associated with Xp11.2 translocation/TFE gene fusion proteins: a case report and review of literature

Jigarkumar Parikh,[1] Teresa Coleman,[2] Nidia Messias,[3] James Brown[4]

[1]Department of Medicine; [2]Department of Medicine, Section of Hematology/Oncology; [3]Department of Pathology; [4]Department of Surgery, Section of Urologic Surgery; Medical College of Georgia, Augusta, GA, USA

Abstract

Xp11.2 translocation renal cell carcinomas (TRCCs) are a rare family of tumors newly recognized by the World Health Organization (WHO) in 2004. These tumors result in the fusion of partner genes to the *TFE3* gene located on Xp11.2. They are most common in the pediatric population, but have been recently implicated in adult renal cell carcinoma (RCC) presenting at an early age. *TFE3*-mediated direct transcriptional upregulation of the Met tyrosine kinase receptor triggers dramatic activation of downstream signaling pathways including the protein kinase B (Akt)/phosphatidylinositol-3 kinase (PI3K) and mammalian target of rapamycin (mTOR) pathways. Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of malignant cells. Here we present a case of a 22-year old female who has been treated with temsirolimus for her Xp11.2/*TFE3* gene fusion RCC.

Introduction

Renal cell carcinoma predominantly manifests after the age of 60 with most cases being sporadic. Most are clear cell carcinomas, with papillary subtypes representing a minority of cases.[1] Abnormalities of the Von Hipple Lindau (*VHL*) gene are found in 40-50% of patients with sporadic RCC, suggesting that the *VHL* gene has a role in pathogenesis.[2] The recently recognized Xp11.2 translocation renal cell carcinomas are accepted as a distinctive entity in the 2004 World Health Organization's renal tumor classification.[1] All bear gene fusions involving the *TFE3* transcription factor gene and comprise approximately one-third of pediatric RCCs.[3]Fusion partners for the *TFE3* gene include the papillary renal cell carcinoma (*PRCC*) gene at 1q21, the splicing factor *PSF* gene at 1p34.1, the splicing factor *NonO* gene at Xp12, and the alveolar soft part sarcoma (*ASPL*) gene at 17q25.[3]

Prognosis in children with TRCC is difficult to ascertain from the literature, but would appear to be favorable for patients with Stage 1-3 surgically resected disease and unfavorable for patients with stage 4 disease.[3-9] The prognosis in adult onset translocation renal cell carcinoma is especially poor. Argani *et al.* analyzed 28 Xp11 translocation RCCs in patients over the age of 20 years.[8] All cases were confirmed by TFE3 immunohistochemistry. Patients ranged in age from 22 to 78 years, with a strong female predominance (female:male ratio 22:6). These cancers tended to present at advanced stage with 14 of the 28 patients presenting with stage 4 disease. Lymph nodes were involved with metastatic carcinoma in 11 of 13 cases in which they were resected.[8] Meyers *et al.* studied 5 cases of translocation carcinoma in adult patients, 18 years or older (mean age 32.6 years). Patients were again diagnosed with advanced disease, and most with distant metastases. Various treatments met with minimal success. Unlike pediatric patients, the adult patients followed a rapidly terminal course, with a mean survival of 18 months after diagnosis in the 3 patients with follow-up data (range 10-24 months).[9] Here we report the successful treatment of adult onset TRCC with an inhibitor of the mammalian target of rapamycin.

Case Report

A 22-year old African American female presented to our institution with a two month history of hematuria, lower extremity swelling, and a 25 lbs (11%) weight loss. On physical examination she had tachycardia, pale oral mucosa, and a palpable mass in the left upper and lower quadrants of the abdomen.

A CT scan of the abdomen and pelvis revealed a 14x14x20 cm necrotic mass in the left kidney with extension through the capsule, tumor invasion into the left renal vein, renal hilar and celiac lymphadenopathy, and four ill defined lesions in the right lobe of the liver measuring 3.3x3.2 cm, 2.4x2.5 cm, 1.6x2.6 cm, and 2.1x1.8 cm, respectively. A CT scan of the chest revealed a 4 mm left lower lobe lung nodule and a small left pleural effusion. A bone scan and brain MRI were negative for metastasis. A subsequent ultrasound guided biopsy of the kidney revealed scant fragments of an epithelioid tumor diagnosed as a renal cell carcinoma. Further classification and grading of the tumor were deferred to the permanent resection. The patient underwent an ultrasound guided alcohol embolization of the left kidney prior to a left nephrectomy, periaortic lymphadenectomy, and caval thrombectomy. At the time of nephrectomy, grossly, a 21x13x12.5 cm mass was noted extending from the hilum of the left kidney to the cortex. Pathological examination of the tumor confirmed a 21x13x12.5 cm mass which occupied the upper pole and middle of kidney extending from the cortex into the renal hilum. The mass grossly extended into the pelvic sinus, involved the renal vein and artery, and invaded into the perinephric fat and Gerota's fascia. The tumor was a mostly solid red/brown to white/tan mass, with a variegated appearance, showing areas of hemorrhage and necrosis, as well as multiple calcified areas. Periaortic lymph node excision revealed that seven of thirty-seven lymph nodes were involved with tumor. The liver lesions were not biopsied intraoperatively due to the highly vascular nature of the tumor. Histopathological examination of the tumor revealed a renal cell carcinoma with a heterogeneous appearance consisting of cells with clear to eosinophilic cytoplasm, arranged in nests and papillary cores, with extensive associated necrosis and hemorrhage. Extensive areas of ossification and focal calcification were also identified. Immunohistochemical analysis of the primary tumor specimen demonstrated the expression of the Xp11.2 translocation/*TFE* gene fusion product, with intense and diffuse positivity. The primary tumor was also focally positive for pancytokeratin, vimentin, CD-10 and negative for EMA. The final pathological staging reported a pT3bpN2pMX TRCC, Fuhrman grade G3, with lymphovascular invasion. Surgical margins were positive at the renal vein and artery, as well as Gerota's fascia. Unfortunately, the patient's post-operative course was complicated by a prolonged hospitalization due to a wound infection.

Eight weeks post operatively the patient began chemotherapy with temsirolimus 25 mg intravenously every week. Before starting chemotherapy the patient developed shortness

Correspondence: Jigarkumar Parikh, 1120 15th Street BAA-5407, Augusta, GA 30912, USA.
E-mail: jparikh@mcg.edu

Key words: renal cell carcinoma; Xp11.2 translocation, temsirolimus.

Received for publication: 12 October 2009.
Accepted for publication: 16 October 2009.

Rare Tumors 2009; 1:e53
doi:10.4081/rt.2009.e53

of breath due to a worsening pleural effusion demonstrated by chest X-ray. Her pleural effusion was presumed to be malignant from metastasis from her primary RCC. The patient unfortunately declined a thoracentesis. The patient responded exceptionally well to temsirolimus clinically and her pleural effusion completely resolved on chest X-ray after four doses of temsirolimus. Significant clinical improvement was also noted with an improvement in appetite, weight gain, resolution of her left flank pain, and a marked improvement in her overall performance status.

Unfortunately after five months of temsirolimus, the patient demonstrated disease progression by CT scanning and recurrence of her pleural effusion. A follow-up CT scan revealed recurrence of her left pleural effusion, a hilar mass, subcarinal lymphadenopathy, and too numerous to count liver lesions. She expired four weeks later after surviving 12 months from the time of diagnosis.

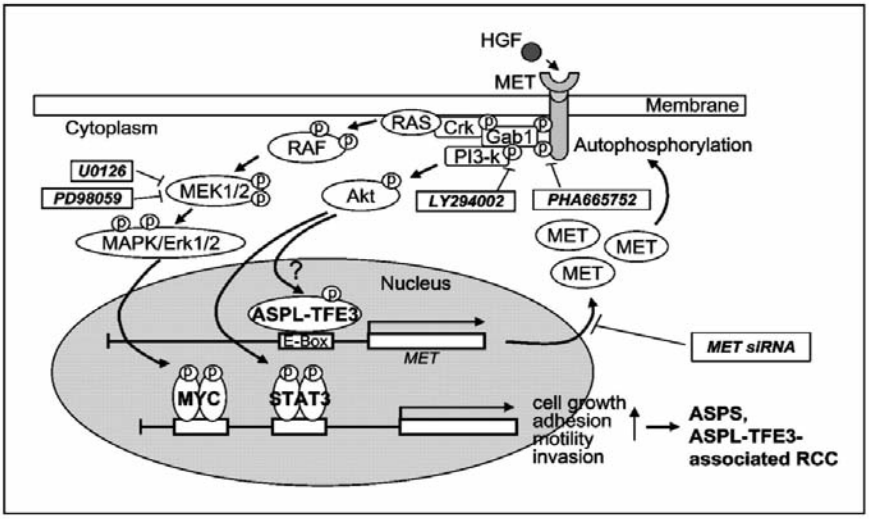

Figure 1. Pro-posed schema of ASPL-TF3-mediated MET activation and downstream effects in ASPL-TFE3-containing human cancers.

Discussion

Translocation renal call carcinomas are usually considered pediatric carcinomas with a strong female predominance.[1-7,10] The WHO describes these cancers as papillary renal cell carcinomas demonstrating translocations involving the *TFE3* gene on chromosome Xp11.2. The histopathological appearance is usually that of a typical papillary carcinoma with clear cells and cells with granular eosinophilic cytoplasm.[1] Early adult onset translocation RCC is associated with an advanced stage at presentation and, most of the time, with metastatic lesions.[9] A mutated *TFE3* gene leads to upregulation of the mesenchymal-epithelial transition (MET) tyrosine kinase receptor that triggers dramatic activation of downstream signaling pathways leading to a neoplastic cascade in normal cells. Thus a therapy that blocks this pathway could represent a reasonable approach to treatment based on biological rationale.

The gene of interest, located at Xp11.2, is *TFE3*, a member of the microphthalmia transcription factor (MiTF) family. Members of this family of genes code for basic-helix-loop-helix leucine-zipper transcription factors that bind DNA as homodimers or heterodimers. *TFE3*-mediated direct transcriptional upregulation of the Met receptor tyrosine kinase triggers dramatic activation of downstream signaling pathways. The depletion of MET by RNA interference or its functional inhibition by a selective inhibitor abolishes hepatocyte growth factor (HGF) stimulated signaling pathways, leading to loss of various tumorigenic phenotypes in *TFE3*-associated renal carcinoma cells, including cell proliferation, adhesion, cell motility, and matrigel invasion [11] (Figure 1).

Many recent publications have linked MET activation to PI3K/Akt signaling.[12-15] PI3K stimulation leads to the activation of mTOR and changes the translation rates of mRNA through the intermediates 4E-BP1 and p 70s6k ribosomal proteins.[13] It has been shown *in vitro* that PI3K activation by growth factors leads to Akt dependant phosphorylation of the E3 ubiquitin ligase Mdm2 and degradation of p53.[14] *In vitro* data also suggest that inhibition of either Mdm2 or mTOR is sufficient to block MET induced cell survival.[13]

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells and the response of such cells to hypoxic stress. Temsirolimus binds to an abundant intracellular protein, FKBP-12, and in this way forms a complex that inhibits mTOR signaling. The disruption of mTOR signaling suppresses the production of proteins that regulate progression through the cell cycle and angiogenesis.[15]

We believe that our patient's improvement with temsirolimus is due to its inhibitory action on mTOR kinase leading to downregulation of cell proliferation and cell growth through two downstream pathways: p70S6K and 4E-BP1.[14] To date, and to our knowledge, there has been no prior report of the use of temsirolimus in Xp11.3/*TFE3* fusion translocation renal cell carcinomas. In our case report we showed resolution of a presumed malignant pleural effusion, weight gain, and a marked improvement in the performance status of the patient after four doses of temsirolimus. We hypothesize that mTOR inhibitors interfere with effects of the *TFE3* gene fusion proteins leading to blockade of some of their prooncogenic effects through the MET receptor tyrosine kinase signaling pathway. *In vitro* data suggest that MEK inhibition enhances rapamycin inhibition of growth in kidney cancer cell lines,[16] and several trials of MET inhibitors and mTor inhibitors are in phase I clinical trials.

TRCCs are usually identified according to their distinct morphology, which is that of a carcinoma organized in nests and papillae lined by clear cells, along with other features such as psammomatous type calcifications.[1] Then, usually only in the setting of a pediatric RCC or an adult who has disease onset at a young age, are TRCCs suspected and immunohistochemical testing for TFE3 carried out. We note with interest that several authors have recently identified TRCCs by TFE3 testing on unusual clinical presentations of RCC that presented with classical clear cell histology.[3,5-7,9] If mTOR/MEK inhibition is proven to be effective in this subclass of renal cell carcinomas, we would ask whether TFE3 testing would be warranted in all cases of RCC in younger patients given the current poor prognosis of patients presenting with advanced stage disease.

References

1. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkail Z. 2004 WHO Classification of the renal tumors of adults. Eur Urol 2006;49: 798-805.
2. Cohen H, McGovern F. Renal cell carcinoma. N Engl J Med 2005;353:2477-90.
3. Altinock G, Kattar M, Mohamed A, et al. Pediatric renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions

and clinicopathologic associations. Pediatr Dev Pathol 2005;8:168-80.
4. Camparo P, Vasiliu V, Molinie V, et al. Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. Am J Surg Pathol 2008; 32:656-70.
5. Perot C, Boccon-Gibod L, Bouvier R, et al. Five new cases of juvenile renal cell carcinoma with translocations involving Xp11.2: a cytogenic and morphologic study. Cancer Genet Cytogenet 2003;143:93-9.
6. Ramphal R, Pappo A, Zielenska M, et al. Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the MiT transcription factor family. Am J Clin Pathol 2006;126:349-64.
7. Carcao M, Taylor G, Greenberg M, et al. Renal cell carcinoma in children: A different disorder from its adult counterpart? Med Pediatr Oncol 1998;31:153-8.
8. Argani P, Olgac S, Tickoo S, et al. Xp11 translocational renal cell carcinoma in adults: Expanded clinical, pathological and genetic spectrum. Am J Surg Pathol 2007;31:1149-60.
9. Meyer P, Clark J, Flanigan R, Picken M. Xp11.2 Translocation renal cell carcinoma with very aggressive course in five adults. Am J Clin Pathol 2007;128:70-9.
10. MC Hintzy, Camparo P, Vasiliu V, et al. Renal carcinoma associated with MiTF/ TFE translocation: report of six cases in young adults. Prog Urol. 2008;18:275-80.
11. Tsuda M, Davis I, Argani P, et al. TFE fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 2007; 67:919-29.
12. Gentile A, Trusolino L, Comoglio P. The Met tyrosine kinase receptor in development and cancer. Cancer Metastasis Rev 2008; 27:85-94.
13. Moumen A, Patane S, Porras A, et al. Met acts on Mdm2 via mTOR to signal cell survival during development. Development 2007;134:1443-51.
14. Adjei AA, Hidalgo M. Intracellular signal transduction pathway proteins as targets for cancer therapy. J Clin Oncol 2005; 23:5386-403.
15. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. Nat Rev Cancer 2004;4:335-48.
16. Costa L, Gemmill R, Drabkin H. Upstream signaling inhibition enhances rapamycin effect on growth of kidney cancer cells. Urology 2007;69:596-602.